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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/493,427	01/29/2000	Patrick L. Iverson	0450-0025.30	2225

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PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/493,427	IVERSON ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,30,32-41,43 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,30,32-41,43 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 3-17-00 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00.

ETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-28-05 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The indicated allowability of claims 28, 30, and 32-40 is withdrawn upon further assessment of the evidence provided in the Weller Declaration.

Response to Amendment

4. The Weller Declaration submitted under 37 CFR § 1.132 is insufficient to overcome the rejection of claims 28-48 based upon 35 USC § 103(a) as set forth in the last Office action because showing is not commensurate in scope with the claims. The unexpected results set forth in the declaration were achieved by using 10 mg oligomer, having a formula as set forth in claim 30, wherein X = $N(CH_3)_2$, Y=O, and Z=O. However, the instant claims are not limited to the particular oligomers used in the Weller Declaration, or to the particular concentration of antisense compound used in the Declaration. Moreover, it is noted that the experiments set forth in the declaration do not include the appropriate controls, such that it would be clear that the same identical conditions were used in the controls as those used to produce the unexpected

results asserted for the claimed morpholino phosphorodiamidate antisense compounds. See discussion below.

Response to Arguments

Claim Rejections - 35 USC § 103

5. Claims 28, 30, 32-41, 43, 45-48 remain rejected and claim 49 is rejected under 35 USC 103(a) as being unpatentable over Zalewski et al. (US Patent No. 6,159,946) in view of Kobayashi et al., Summerton et al. (US Patent No. 5,378,841), Burger, and Agrawal et al. for the reasons of record set forth in the Office Action mailed 3-19-04, and those reasons set forth below.

6. Applicant's arguments filed 2-28-05 have been fully considered but they are not persuasive. Applicants traversed the rejection of claims 41, 43, and 45-48 by way of amending the claims to recite a method for treating a vascular injury site in a human patient comprising providing an intravascular stent. Upon further consideration, the Weller Declaration submitted under 37 CFR § 1.132 and filed May 01, 2003, is not considered commensurate in scope with the claimed invention. For example, claim 28 encompasses a method for treating a vascular injury site in a human comprising administering a morpholino antisense compound having uncharged phosphorodiamidate intersubunit linkages and comprising the sequence identified as SEQ ID NO: 1. The unexpected results set forth in the declaration were achieved by using 10 mg oligomer, having a formula as set forth in claim 30, wherein X = $N(CH_3)_2$, Y=O, and Z=O. However, claim 28 is not limited to the particular oligomers used in the Weller Declaration, or to the particular concentration of antisense compound used in the Declaration. Moreover, it is noted that the experiments set forth in the declaration do not include the appropriate controls,

such that it would be clear that the same identical conditions were used in the controls as those used to produce the unexpected results asserted for the claimed morpholino phosphorodiamidate antisense compounds. Although Applicants mention that the conditions used in the Weller Declaration were *generally* comparable to the AVI Biopharma study of Kutryk et al. using a phosphorothioate modified c-myc oligonucleotide, it is not immediately apparent that the same results would have been produced using *identical* conditions as those used in the current study. In order for results to be considered unexpected, Applicants must provide a means for judging the practical significance of data set forth in the Declaration (see MPEP § 716.02). In the instant case, Applicants allege that conditions used in the Kutryk et al. reference were generally comparable to those used in the instant case. However, in order to properly judge whether or not Applicant's results are truly unexpected over the prior art, applicants must provide evidence that in a side by side comparison, using identical conditions, the full scope of the claimed methods using morpholino modified phosphorodiamidate antisense compound comprising SEQ ID NO: 1, unexpectedly produce a greater reduction in restenosis in comparison to the prior art phosphorothioate modified antisense compound comprising SEQ ID NO: 1. In the instant case, since there are no control oligonucleotides representing the prior art modified oligomers under the same conditions as those used to produce the asserted unexpected results, the relevance of data set forth in the Weller Declaration cannot be properly judged as being unexpected.

Furthermore, although the Kutryk et al. reference did not observe any reduction in restenosis in patients treated with phosphorothioate-modified c-myc antisense oligonucleotides, Kalewski et al. were granted US Patent 6,159,946 which claims a generic method for inhibiting proliferation of smooth muscle cells in restenosis, comprising the step of locally administering c-

myc antisense in a porous balloon catheter. The disclosure of Kalewski et al. also demonstrates inhibition of restenosis in a porcine model of restenosis using a phosphorothioate modified c-myc antisense compound (which comprises 14 contiguous nucleobases of SEQ ID NO: 1). It is further disclosed in the prior art that morpholino modified antisense compounds are useful for the treatment of restenosis in a patient, see Burger which teaches the reduction of restenosis in an animal comprising the administration of morpholino modified oligomers via a biodegradable stent.

Therefore, as stated in the prior Office Action mailed 3-19-2004, absent evidence to the contrary, it would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to modify the method of preventing restenosis in a patient as described by Zalewski et al. with the antisense oligonucleotide of Kobayashi et al. because this antisense oligonucleotide has been disclosed to function successfully in vitro and in vivo to reduce the expression of c-myc. Furthermore, one of skill in the art would have been motivated to use the antisense oligonucleotides of Kobayashi et al. (which comprises SEQ ID NO: 1 of the instant invention) because it would have been obvious to replace one functionally equivalent antisense oligonucleotide targeting c-myc with another. Additionally, absent evidence to the contrary it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Zalewski et al. to comprise the administration of antisense oligonucleotides comprising internucleoside linkages having morpholino modifications as taught by Summerton et al. and Burger, and to comprise the use of a biodegradable stent as taught by Burger. One of ordinary skill in the art would have been motivated to use morpholino modified oligomers of Summerton et al. or Burger, because Burger clearly teach the reduction of

restenosis in an animal comprising the administration of morpholino modified oligomers via a biodegradable stent. Furthermore, absent evidence to the contrary, it would have been obvious to one of ordinary skill in the art to modify the oligonucleotides of Zalewski et al. with triethyleneglycol modifications as described by Agrawal, since these modifications enhance the solubility of the antisense oligonucleotides.

Moreover Applicant's method recites the use of an antisense compound in an amount of about 0.5 to 2 mg or in a solution containing at least about 30 mg/ml. Zalewski et al. teach the use of antisense oligonucleotides in their disclosed methods in amount of between about 1 to 100 μM and more preferably between 1 to 10 μM. Although the method of Zalewski et al. does not recite the exact amount of antisense compound as recited in Applicant's method, absent evidence to the contrary it would have been obvious to one of ordinary skill in the art to optimize the conditions of an experiment or reaction in order to maximize the desired results.

Therefore, the invention as a whole is *prima facie* obvious Zalewski et al. (US Patent 6,159,946) in view of Kobayashi et al., Summerton et al., Burger, and Agrawal et al.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

JLE